REMARKS

Claims 46, 49-62, 65, 89 and 90 are pending in the subject application. Claims 52, 54, 55 and 90 are canceled hereinabove without disclaimer or prejudice to applicants' right to pursue the subject matter of these claims in the future. In addition, claims 46, 49-51, 62 and 89 have been amended hereinabove to more clearly define the subject matter applicants are claiming in this application. Support for the amendment to the claims may be found throughout the specification, as well as in the claims previously presented.

Applicants maintain that this Amendment raises no issue of new matter and request entry of this Amendment. Upon entry of this Amendment, claims 46, 49-51, 53, 56-62, 65, and 89 will be pending and under examination.

A. Acknowledgement of August 1 and August 6, 2007 Interviews

As an initial matter, applicants wish to thank the Examiner for the courtesy extended during the telephone interview on August 1, 2007 concerning the effective filing date issue and during the in-person interview on August 6, 2007, also attended by Dr. David Pinsky, one of the named inventors. Applicants believe these interviews were most helpful in clarifying the issues in the March 27, 2007 Office Action and have attempted to address these issues in this response.

B. Rejection Under 35 U.S.C. §112, First Paragraph On The Ground Of Lack Of Enablement

In rejecting applicants' claims for an asserted lack of enablement, the Examiner made the following points:

1. the specification, while enabling for an organ donor to be sacrificed, did not enable a healthy donor or an organ recipient;

2. carbon monoxide is a toxic gas;

3. citing Dolinay, et al. "It remains unclear how to define a safe dose of CO for human therapy";

4. animal models are not predictive of success in humans; and

5. undue experimentation would be required to use applicants' invention.

In response, applicants initially note that these matters were discussed at length during the interview on August 6, 2007. As indicated in the Interview Summary for that interview, the Examiner agreed to reconsider his position after all the evidence and arguments discussed are formally filed.

With respect to the points made by the Examiner, applicants note the following:

1. The specification discloses experiments with healthy

animals to which carbon monoxide was administered. These experiments included both lung transplant experiments (Example 11; page 133-136) and experiments involving a model of stroke (Example 7, pages 110-112). The former experiments involved healthy rats and the latter involved healthy mice. In each of these experiments, the administration of CO was not toxic to the animals tested. In the former, only one lung was removed and the rats survived until they were euthanized in accordance with the experimental protocol. In the latter experiment, the mice produced large amounts of endogenous CO which conferred cerebral protection that limited the amount of tissue destroyed during stroke. Thus, these experiments clearly show that CO can be administered to a healthy subject, whether organ donor or recipient.

2. Although exogenous carbon monoxide can be a toxic gas at certain concentrations, it is produced endogenously without toxic effect and the effects of CO at varying doses are well established. Thus, organizations such as the U.S. Environmental Protection Agency, the U.S. Department of Labor, and the World Health Organization has published information concerning non-toxic levels of CO to which humans may be exposed. See Exhibits A, B and C attached hereto.

Moreover, in Bathoorn, et al., "Effects of low dose inhaled carbon monoxide in patients with COPD", the authors reported that administration of inhaled 95 ppm CO for two hours on 4 consecutive days to stable COPD patients was well tolerated. See Exhibit D attached

hereto, Abstract P3840, pg. 661s.

Furthermore, as was discussed with the Examiner during the August 6, 2007 interview, the U.S. Food and Drug Administration has approved an Investigational New Drug Application (IND) submitted on behalf of applicants' licensee, INO Therapeutics, authorizing a study of inhaled CO to recipients of kidney transplants based on data establishing that CO could be safely administered. See Exhibit E attached hereto.

3. As demonstrated *inter alia* by Exhibits A-E, it is clear how to define a safe dose of CO for human therapy. The passage of Dolinay, et al. quoted by the Examiner is simply incorrect. Importantly, Dolinay also states, "Despite its reputation as a noxious gas, CO may well be on its way to providing a low cost and effective therapy for a number of disease conditions. Collectively, the body of research described herein heralds the future exploitation of CO in the clinic for the treatment of advanced-stage lung disease, and the improved success of organ transplantation."

4. Animal models are predictive of success in transplantation. The Examiner's reliance on statements by Ryter, et al. and Mayr, et al. is misplaced. First, Mayr, et al. is concerned with endotoxin response, not transplantation. In transplantation, animal models have been used successfully to establish surgical procedures for decades, as well as to successfully predict the efficacy of organ preservation solutions and

immunosuppressive therapies. Second, Ryter, et al. only comment on the presumed regulatory difficulties of obtaining approvals for studies in humans. Ryter, et al. do not support any rejection on the basis of lack of enablement or the lack of predictability based on animal experiments.

5. Undue experimentation is not required to enable applicants' claimed invention, particularly having regard to the CO dose now recited in the amended claims which would clearly not be toxic, particularly given the information provided in Exhibits D and E.

In summary, applicants maintain that their specification clearly enables their invention as now claimed and respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, first paragraph, for alleged lack of enablement.

C. Rejection Under 35 U.S.C. §112, First Paragraph On The Ground Of Lack Of Written Description

On pages 5-10 of the March 27, 2007 Office Action, the Examiner again rejected applicants' claims for lack of written description, initially reiterating the reasoning set forth in the previous Office Action dated June 26, 2006 and then on pages 8-10, reiterating comments concerning various publications which appeared in the rejection for lack of enablement discussed above as the basis for rejecting the Declaration of Dr. Kron dated December 20, 2006.

As was discussed during the August 6, 2007 interview, the

specification clearly contemplates that the subject to whom CO is administered may be an organ donor. See particularly Example 11 on pages 133-136. Alternatively, CO may be administered to the recipient of a transplanted organ. In this regard, applicants directed the Examiner's attention during the August 6, 2007 interview to the disclosure on page 20, lines 22-36, which states that carbon monoxide may be administered to the subject up to about 1 day after surgery to lessen the manifestation of an ischemic disorder. See also claim 56. Clearly, administration after surgery to lessen manifestation of an ischemic disorder contemplates that the subject is the recipient of the transplanted organ. Applicants during the interview understood that the Examiner had not appreciated this passage on page 20 of the specification and would reconsider his rejection in view of this disclosure. Finally, the conclusion that "subject" includes both an organ donor and organ recipient is fully supported by the Declaration of Dr. Kron previously submitted which is incorporated by reference into this response.

With respect to the various references relied upon by the Examiner, none relate to the content of applicants' specification and therefore cannot be evidence that rebuts Dr. Kron's Declaration which expressly concerns applicants' specification and the understanding which one skilled in the art would have of its contents including specifically the meaning of "subject" as of its filing date.

Finally, as discussed during the August 6, 2007 interview, applicants have amended claim 46 to address concerns the Examiner had as to the presence or absence of an adequate written description for the specific claim language previously presented in

the claims.

In view of the preceding comments, applicants request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, first paragraph, for an asserted lack of written description in view of the amendments to the pending claims and the preceding remarks.

D. Effective Filing Date of the Subject Application

1. Applicant Is Clearly Entitled To An Effective Filing Date Of At Least April 1, 1998 For The Subject Matter Now Claimed

As discussed during the August 1, 2007 telephone interview and as indicated on the copy of the filing receipt attached hereto as Exhibit G, the subject application claims the benefit of the April 1, 1998 filing date of U.S. Serial No. 09/053,871, issued as U.S. Patent No. 6,315,995 on November 13, 2001. U.S. Serial No. 09/671,100 was amended to withdraw the claim for benefit of the September 27, 1996 filing date of U.S. Serial No. 08/721,447 and the September 25, 1997 filing date of PCT/US97/17229. However, U.S. Serial No. 09/671,100 was not amended to withdraw the claim to benefit of U.S. Serial No. 09/053,871.

As filed, U.S. Serial No. 09/053,871 incorporated by reference the disclosures of U.S. Serial No. 08/721,447 and PCT/US97/17229, i.e., the identical disclosure relating to carbon monoxide now written out explicitly in the subject application. Accordingly, U.S. Serial No. 09/053,871, by virtue of this incorporation by reference contained the complete disclosure relating to carbon monoxide now

at issue. See M.P.E.P. 2163.07(b). Therefore, the subject application is entitled to an effective filing date of at least April 1, 1998 for the carbon monoxide subject matter being claimed.

2. Applicant Is Entitled to The Benefit Of The September 27, 1996 Filing Date of U.S. Serial No. 08/721,447 And The September 25, 1997 Filing Date of PCT/US97/17229

As discussed during the August 1, 2007 telephone interview with the Examiner, applicants maintain that the subject application is entitled to the benefit of the filing date of U.S. Serial No. 08/721,447 and PCT/US97/17229 for at least the following reasons:

(a) Contrary to the Examiner's statement at the bottom of page 11 and the top of page 12, U.S. Serial No. 09/671,100 did refer to and claim the benefit of the earlier filing date of U.S. Serial No. 08/721,447 and PCT/US97/17229 at the time U.S. Serial No. 09/671,100 was filed. In fact, as the Examiner acknowledges, this benefit claim was present but was amended to withdraw the benefit claim. 35 U.S.C. §120 only requires that an application be copending with and refer to an earlier copending application in order to claim benefit of the earlier application's filing date.

It is undisputed that as of the December 27, 2000 filing date of U.S. Serial No. 09/671,100, U.S. Serial No. 09/053,871, filed April 1, 1998, was pending (only issued as U.S. Patent No. 6,315,995 on November 13, 2001). It is also undisputed that U.S. Serial No. 09/053,871, filed April 1, 1998, was copending with (i) U.S. Serial No.

08/721,447, filed September 27, 1996 and only abandoned on August 11, 2000, and (ii) PCT/US97/17229, filed September 25, 1997 with a 30-month national stage entry deadline of March 25, 2000. Thus, it is undisputed that all applications in question were copending.

It is also undisputed that, as filed, U.S. Serial No. 09/671,100 in its first paragraph referred to all the applications listed on the filing receipt attached hereto as Exhibit G.

In denying applicants the benefit of the filing dates of 08/721,447 and PCT/US97/17229, the Examiner has added a new requirement for claiming benefit under 35 U.S.C. §120 with is not present in the statute, not present in 37 C.F.R., and not supported by any case law (and the Examiner had cited no such support). Specifically, the Examiner has added the requirement that the reference to the prior application(s) must have been maintained during the pendency of 09/671,100. Applicants respectfully disagree and maintain that there is no legal basis for such a requirement.

Accordingly, applicants request that on this basis, the Examiner reconsider his position and acknowledge the validity of applicants' claim for the benefit of the September 27, 1997 filing date of 08/721,447 and the September 25, 1997 filing date of PCT/US97/17229.

(b) The Incorporation By Reference In 09/671,100 Of The Contents Of Each Of 09/053,871 and PCT/US99/07175

Resulted In A Reference To 08/721,442 and PCT/US97/17229

As discussed in M.P.E.P. 2163.07(b), an incorporation by reference is equivalent to writing out all the contents of the documents so incorporated. Each of 09/053,871 and PCT/US99/07175 expressly refers to both 08/721,447 and PCT/US97/17229. U.S. Serial No. 09/671,100 incorporated by reference each of 09/053,871 and PCT/US99/07175 and was copending with each of these applications. Therefore, 09/671,100 refers to each of 08/721,447 and PCT/US97/17229 by virtue of the incorporation by reference of US/053,871 and PCT/US99/07175. Since there is no question being raised as to copendency, only a question as to the adequacy of the reference to the earlier application, these references to the earlier applications suffice for purposes of 35 U.S.C. §120.

Accordingly, applicants request that the Examiner reconsider his position and acknowledge the validity of applicants' claim for benefit of the filing dates of 08/721,447 and PCT/US97/17229.

E. Bach, et al. (US2003/0039638) Is Not Prior Art Under 35 U.S.C. §102(a) or (e) or §103(a)

As noted above, applicants' entitlement to the benefit of the April 1, 1998 filing date of U.S. Serial No. 09/053,871 is undisputed. Moreover, U.S. Serial No. 09/053,871 clearly incorporated by reference the carbon monoxide disclosure present in the subject application by its reference to 08/721,447 and PCT/US97/17229. Accordingly, applicants are clearly entitled to an effective filing date of at least April 1, 1998 for the subject matter now being claimed. Based on an April 1, 1998 effective filing date, Bach, et al. is not prior art as to applicants' currently claimed invention.

Accordingly, applicants request that the Examiner reconsider and withdraw all rejections over Bach, et al.

F. Supplemental Information Disclosure Statement

This Information Disclosure Statement is submitted to supplement the Information Disclosure Statements filed October 3, 2003; June 15, 2004; September 16, 2004; December 30, 2004; April 10, 2006; August 11, 2006; and December 26, 2006. In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following references which are also listed on the attached substitute Form PTO-1449 attached hereto as Exhibit H.

1. Printout from U.S. Environmental Protection Agency website <http://epa.gov>; Green Book entry for carbon monoxide, revised as of July 1, 2001 (Exhibit A);

2. Printout from U.S. Department of Labor website <http://www.osha.gov>; Occupational Safety and Health Guidelines for Carbon Monoxide, printed August 1, 2007 (Exhibit B);

3. Printout from World Health Organization website <http://www.euro.who.int/document/aiq/5_5carbonmonoxide.pdf>; Air Quality Guidelines, 2nd Edition, Chapter 5.5 (2000) (Exhibit C);

4. Bathoorn, et al. "Effects of low dose inhaled carbon monoxide in patients with COPD" Recent advances in the treatment of

COPD and acute lung injury, abstract P3840, p. 661s (2006) (Exhibit D);

5. Investigational New Drug Application submitted October 20, 2006 under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Covox™ (carbon monoxide) single dose inhalation for INO Therapeutics (Exhibit E); and

6. U.S. Patent No. 7,238,469 B2 of Bach, F., et al., issued July 3, 2007 (Exhibit F).

Applicants request that the Examiner consider these references, initial the attached substitute Form PTO-1449 and make the references of record in the subject application.

G. Summary

In view of the amended claims and the remarks set forth above, applicants respectfully request that the Examiner reconsider and withdraw all rejections set forth in the March 27, 2007 Office Action and allow this application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $1020.00 fee for a three-month extension of time and $180.00 fee for filing a Supplemental Information Disclosure Statement under 37 C.F.R. §1.17(p), is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

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EXHIBIT H